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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,567	03/19/2002	Shizuo Akira	14119.105010	3078

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
02/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Advisory Action Before the Filing of an Appeal Brief	Application No. 10/088,567	Applicant(s) AKIRA ET AL.	
	Examiner Anoop Singh	Art Unit 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 January 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *35 and 38*.
   Claim(s) withdrawn from consideration: *8-16,21-30 and 32-34*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). 1/9/2008
13. ☐ Other: _____.

/Thaian N. Ton/
Primary Examiner
Art Unit 1632

Continuation of 5. Applicant's reply has overcome the following rejection(s): Claims 35 and 38 rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility is withdrawn. Applicants' argument filed 1/9/2008 have been fully considered and are persuasive to the extent Examiner would agree with applicants submission of reference of Zimmerman et al that shows the treatment of infected mice with a nucleotide sequence identical to TLR9 provides a protective and curative response in the mice and thus provides some general utility of the mouse against parasitic infection. However, Applicants' argument that the utility of the knockout mice and cells according to the invention for screening treatments against "bacterial infection" such as "Leishmania major" is specific, substantial and credible is not persuasive because Leishmania major is not a bacterial infection rather it is parasitic infection. Although specification does not contemplates role of TLR9 in parasitic infection, however applicants submission provide adequate general utility of the mouse in parasitic infection and therefore utility rejection is withdrawn.

Continuation of 11. does NOT place the application in condition for allowance because: The Examiner maintains the rejection of claims 35 and 38 under 35 U.S.C. 112, first paragraph, for the reasons of record. Applicants rebut the rejection of the claims under 35 USC 112, first paragraph, in the reply filed 1/9/2008. Applicants' argument filed on 01/09/2008 have been fully considered but they are not fully persuasive for the reasons of record.

Claims 35 and 38 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicants' argues that Experiment 4 provides a specific example of screening for agonists of TLR9 which can be useful in the treatment of bacterial infection (see page 21, line 26 through page 23, line 29). Applicants assert that it is known in the art to use SEQ ID NO.5 against L. major infection (see Zimmerman cited above). Therefore, one of skill in the art with the instant specification (see Experiment 4) in hand would be enabled for screening additional treatments against L. major infection using the knockout mice and cells according to the invention.
In response, it is noted that claim 35 is directed to a transgenic mouse whose genome comprises a homozygous inactivation of TLR9 allele such that no functional N-terminal fragment of TL9 is produced and wherein macrophage of said mouse shows decreased responsiveness to CpG ODN. Applicants' argument against utility as well as enablement rejection centers around the reference of Zimmerman et al Journal of Immunology, vol. 160, 3627-3630, 1998 showing protective and curative effect of TLR9 in the mice against "bacterial infection" such as "Leishmania major" (see arguments in support of utility and enablement). It is emphasized that contrary to applicants' argument L. major is not bacterial infection rather it is parasitic infection. The teaching of Zimmerman et al provides evidence of role of TLR9 against parasitic infection but fails to establish any nexus with bacterial infection. The specification contemplates knockout mice lacking TLR9 could be used to elucidate functional mechanisms of bacterial DNA and others having an unmethylated CpG sequence and to developing vaccine against bacterial infections (page no 14) and identify agonist or antagonists. Examiner has previously indicated that DNA vaccine elicits immune responses by multiple mechanisms and role of TLR9 is not essential for the induction of immune responses following DNA immunization. It is apparent that instant specification has not provided adequate guidance as to how an artisan would have used the TLR knockout mouse in developing vaccine against bacterial infection. There is no specific teaching as to the role of TLR9 in a particular bacterial disease or disorder. The specification discloses no nexus between TLR9 and any known bacterial pathological state nor does provide adequate guidance how it could be used in screening agonist or antagonist for developing any vaccine against bacterial infection. Examiner has previously indicated that the specification asserts multiple uses for the claimed transgenic knockout mouse and cells for screening of agonist or antagonist, developing vaccine against bacterial infection or to diagnose and treat bacterial diseases and also elucidate functional mechanisms of DNA derived from bacteria at the molecular level (see page 25, para. 2). The specification does not provide specific guidance teaching how to use a mouse that has claimed phenotype, for reasons of record. Disclosure of a phenotype is not sufficient to teach how to use the claimed animal. The specification suggests that an animal having the claimed phenotype could be used to identify agonist or antagonist of receptor protein recognizing bacterial DNA having an unmethylated CpG sequence, but there is absolutely no guidance with regard to how to use a TLR9 knockout animal in such assays, to successfully identify agonist or antagonist that have the desired activity. An artisan would not know whether macrophage having reduced reactivity to unmethylated CpG sequence is due to TLR9 knockout or it is because of other compensatory factors. The specification does not establish nexus between TLR9 knockout to the immune response generated against any bacterial infection as discussed in previous office action. Additionally, role of TLR9 in parasitic infection as described in prior art and argued by applicants fails to establish the nexus between effect of TLR9 in bacterial infection. It is apparent that instant specification has not provided any guidance as to how an artisan would have used the TLR knockout mouse in bacterial infection as described in this application. In absence of any specific teaching an artisan would have to perform undue experimentation to make and use of the invention. It is emphasized that there is no teaching as to how to use the claimed animals for any other purpose other then against bacterial infection. Thus, the specification fails to provide an enabling disclosure for using the claimed animals and practicing the claimed screening methods, for reasons of the record.

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